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TITLE: Pathophysiologic Impact of Doxorubicin and Radiation Therapy on the Heart of Patients Treated for Breast Cancer

PRINCIPAL INVESTIGATOR: Patricia H. Hardenbergh, M.D.

RECIPIENT ORGANIZATION: Duke University Medical Center
Durham, North Carolina 27710

REPORT DATE: July 1999

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PREPARED FOR: Commander
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Fort Detrick, Frederick, Maryland 21702-5012

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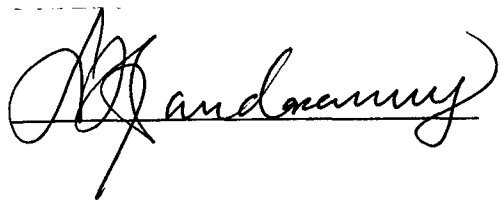

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13. ABSTRACT ***(Maximum 200 Words)***

Purpose: To assesses the incidence and extent of radiation induced regional cardiac perfusion defects and functional abnormalities in patients with left-sided breast cancer following RT with and without chemotherapy.

Methods: Fifty-one patients with left-sided breast cancer have undergone pre-treatment (SPECT) cardiac perfusion scans to evaluate regional myocardial perfusion and cardiac function by LVEF. At six month intervals the patients have follow-up perfusion scans and physical exams for a minimum of 2 years. Radiation doses and heart/left ventricle volumes are calculated on a computed tomography (CT) based 3-D treatment planning system (PLUNC).

Results: Thirteen patients have had a 6 month follow-up cardiac perfusion scan. Eight of thirteen patients have a new visibly detectable perfusion defect on the post radiation scan in the anterior region of the left ventricle which correlates with the tangential radiation beams. There appears to be a dose-dependent change with a 20% reduction in perfusion in the volume of heart receiving 40-50 Gy. No patient has had a change in their LVEF or evidence of functional defect in the heart.

Conclusion: It appears that radiation causes a dose-dependent regional cardiac perfusion defect in 60% of patients studied. To date these changes do not correlate with function or clinical sequelae.

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DUKE UNIVERSITY MEDICAL CENTER
Department of Radiation Oncology

July 29, 1999

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Sincerely,

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FOREWORD

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Patricia Hardenbergh 8/6/95

PI - Signature Date

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INTRODUCTION:

In the primary management of breast cancer, radiotherapy is playing an increasingly important role and, as a result, there has been more concern about long-term side effects of radiation. Cardiac complications in patients with breast cancer have been thought to be caused by ischemic heart disease, with a time of onset of several years after the radiotherapy (1). Some series of post-mastectomy radiated patients have demonstrated an excess number of cardiovascular deaths in the radiated group (2).

The concern for cardiotoxicity is complicated by the widespread use of adjuvant systemic therapy, in particular anthracycline-containing drug regimens. Doxorubicin is a well known cardiotoxin, the principle effects being on the myocardium with an increasing incidence of congestive heart failure (CHF) correlated with increasing doses (3). Radiotherapy to the heart in conjunction with doxorubicin appears to increase the risk of developing cardiac damage (4). Therefore, additional investigations into cardiac toxicity of radiation in combination with chemotherapy are timely and appropriate.

Conventional radiation treatment planning involves calculating radiation dose in a single plane or, at most, in two to three planes. Although generally adequate for most clinical situations, it does not enable one to quantitatively determine the volume of a given organ irradiated or the dose received by that organ, particularly when the field arrangement is complex and the dose distribution heterogeneous. Most reports in the literature describing radiation induced heart disease have been unable to indicate the dose and volume of heart irradiated with precision (5,6). New three-dimensional (3D) radiation treatment planning tools now provide the opportunity to know the dose distribution in any tissue precisely.(7) Furthermore, 3D planning software allows for dose calculation from complex field arrangements with the ability to correct for density differences within any tissue. Thus, a dose volume histogram may be generated for any organ of interest giving us the dose of radiation received by the various portions of that organ. Advances in image registration allow us to superimpose the 3D dose distribution onto noninvasive nuclear medicine 3D cardiac imaging studies (8).

In this work, we will exploit recent advances in 3D radiation treatment planning with 3D functional nuclear medicine imaging to better understand the physiologic effects of radiation on regional heart function. We will relate the regional radiation dose and volume of heart irradiated to subsequent regional perfusion changes, the latter being used as a surrogate for both myocardial damage and coronary artery blood flow. Changes in organ function assessed by subclinical (ejection fraction) and clinical (congestive heart failure) endpoints will be related to the degree and extent of change of regional perfusion. The findings from this study may impact on standard treatment recommendations for patients receiving radiotherapy and chemotherapy for left-sided breast cancer.

Specific hypothesis to be tested include:

Hypothesis 1: A radiation dose and volume dependent reduction in regional cardiac perfusion will be observed within 18-24 months following radiation therapy.

Hypothesis 2: The changes in regional cardiac perfusion will be enhanced in patients who have received chemotherapy and radiotherapy compared to patients treated with radiotherapy alone.

Hypothesis 3: Changes in ejection fraction after chemotherapy and radiotherapy are related to the extent and degree of regional perfusion changes.

Hypothesis 4: The use of 3D computer assisted radiotherapy planning may result in a reduction of radiation dose to the heart compared with conventional 2D planning while not reducing coverage of the tumor region itself.

BODY:

Methods:

All patients with left-sided breast cancers undergoing radiation therapy are eligible. Appropriate informed consent is obtained prior to enrollment.

Prior to initiation of chemotherapy, and at the completion of chemotherapy, prior to the initiation of radiotherapy, the following studies are performed:

1. Rest radionuclide angiography to determine cardiac ejection fractions.
2. Rest Tc-99m sestamibi SPECT cardiac perfusion scan to provide a 3D map of the regional cardiac perfusion.
3. A thoracic CT scan in the treatment position for 3D treatment planning and dose calculation is done once prior to radiotherapy.

Follow-up evaluations will be performed at 6-month intervals following completion of radiotherapy for a period of two years. At the time of follow-up the following studies will be performed:

1. Ejection fractions assessed by first-pass radionuclide angiography.
2. Rest Tc99m sestamibi SPECT cardiac perfusion scans.
3. Clinical evaluation to assess tumor status and any cardiac symptoms or disease.

Using the pre-radiation CT scan, a 3D radiation dose calculation, with lung density correction, will be done to determine the radiation dose delivered to the heart. Computer software (Plan University of North Carolina) will be used to visually register the SPECT cardiac images with the pretreatment CT cardiac contour. The entire 3D radiation dose distribution is then overlaid onto the SPECT scan. By calculating the number of SPECT counts on each radiation dose level, a dose-count histogram is generated. Dose-count histograms are calculated for all of the SPECT scans. The reduction in percent of the SPECT counts at a particular dose level (compared to the pretreatment scan) is calculated at each dose level. We will compare changes in regional perfusion by calculating dose count histograms by this method. The reduction in percent of SPECT counts will be examined at a particular radiation dose level with respect to the chemotherapy dose received for a patient.

Results:

At present 51 patients with left-sided breast cancer have been enrolled on the study. This has exceeded our estimated planned accrural rate of 30 patients/year. The patient's age range is from 36 to 81 years old. The racial distribution includes 39 white patients, 7 African-American patients, 1 Hispanic-American patient, and 4 unknown racial orientation. To date, two patients have withdrawn from the study prematurely. The distribution of treatment of patients enrolled on the study include: 20 patients will undergo radiation therapy only, 31 patients are being treated with a combination of radiation and chemotherapy. The prescribed tangent RT dose was 46 Gy for all patients. The percent volume of heart and left ventricle irradiated at the 50% isodose line ranged from 1.8 to 10% and 2.9 to 19% respectively. Thirteen patients have had an initial 6 month follow-up cardiac perfusion scan.

Hypothesis #1: To date, 8 of the 13 patients with six month follow-up post-radiation perfusion imaging have a new visibly detectable perfusion defect on the post RT scan. All 8 patients have a new perfusion defect in the anterior region of the left ventricle which correlates with the tangential RT beams. Four of these 8 patients with new perfusion defects have received Adriamycin chemotherapy. Correlating the dose distribution with pre and post RT SPECT scans in five patients who received radiation therapy to the breast identified a dose-dependent reduction in the regional cardiac perfusion, R^2=.90. There was no evidence of reduction in regional cardiac perfusion in the volume of the heart receiving 10 Gy, a 10% reduction in perfusion in the volume of the heart receiving 20-30 Gy, and a 20% reduction in perfusion in the volume of the heart receiving 40-50 Gy.

Hypothesis #2: At present with only 8 patients to evaluate, our numbers are too small to detect a difference between patients who are receiving both chemotherapy and radiation versus radiation alone.

Hypothesis #3: Of the 13 patients with 6 month follow-up cardiac perfusion scan, none have had a decrease in their left ventricular ejection fraction regardless of the extent or degree of regional perfusion changes. This may be preliminary evidence that although radiotherapy is inducing regional perfusion changes in some patients, the function of the heart is not compromised.

Hypothesis #4: A subset of patients have undergone comparison of 2D radiation planning to 3D radiation planning. Presently 20 patients have been evaluated. Of these, 10 patients had radiation therapy to the left side with the inclusion of internal mammary nodes, 10 patients had radiation therapy to the left breast without including regional lymph nodes. Of the patients who had radiation therapy planned to include the internal mammary nodes (IMN) 10 of 10 appeared to benefit from the 3D treatment planning when analyzed with respect to dose volume histograms of the heart and the target tissue. The heart was blocked from the radiotherapy beam more successfully in the radiation treatment plans where 3D treatment planning was used. This was an improvement over the 2D radiation planning. Additionally, all 10 patients with planned IMN RT had an improvement in the IMN target coverage when the 3D radiation planning was performed. Patients who did not have IMN planned in the radiation therapy field did not appear to have a measurable difference in comparing the 2D versus the 3D radiation treatment planning. These results are preliminary.

KEY RESEARCH ACCOMPLISHMENTS:

- Radiation appears to cause a dose dependent regional cardiac perfusion defect in some patients.
- Regional perfusion changes from radiation do not correlate with a change in cardiac function or cardiac events.
- It is unclear whether chemotherapy influences the extent or degree of regional perfusion defects.
- 3D radiation planning has an important role in treatment planning of patients with internal mammary nodes included within the radiation field.

REPORTABLE OUTCOMES:

American Society of Therapeutic Radiation Oncology Platform presentation, October, 1999, San Antonio, TX

Abstract: Pathophysiologic Impact of Doxorubicin (Dox) and Radiation Therapy (RT) on the Heart of Patients Treated for Breast Cancer.

CONCLUSIONS:

This cardiac toxicity study was designed to assess the incidences of regional cardiac perfusion defects, as well as functional abnormalities in patients with left sided breast cancer following radiation with or without chemotherapy. In addition, the study examines the extent of RT-induced changes in the regional perfusion and attempts to determine whether it is related to cardiac volume irradiated, cardiac function, or clinical sequelae.

To date, at 6 months follow-up radiation appears to cause a dose-dependent regional cardiac perfusion defect in 60% of the patients studied (8/13). To date, these regional perfusion changes do not correlate with a change in left ventricular ejection fraction or clinical cardiac events. To date it does not appear that Adriamycin chemotherapy influences the extent of regional perfusion defects, however at this point in the study our numbers are too small. This is an ongoing study and updated results will be reported with longer follow-up and more extensive information on patients who are treated with combined modality of doxorubicin and radiation. It appears that 3D radiation treatment planning for left-sided breast cancer has an important role for improving treatment planning in patients who the internal mammary nodes are included in the radiation field. Three-dimensional planning in this group of patients limits the volume of heart irradiated and improves coverage on the target.

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APPENDIX I

NAME

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Presenting Author:	Dr. Patricia H. Hardenbergh
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Notes:	• The name: **P. H. Hardenbergh** appears as a contributing author on **2 submitted abstracts.**

Abstract created on 4/9/99 at 9:38:30 AM.

Abstract Title: PATHOPHYSIOLOGIC IMPACT OF DOXORUBICIN (DOX) AND RADIATION THERAPY (RT) ON THE HEART OF PATIENTS TREATED FOR BREAST CANCER

Presenting Author: Dr. Patricia H. Hardenbergh

Contributing Authors: Hardenbergh PH[1], Munley MT[1], Bentel GC[1], Strickland J[1], Borges-Neto S[2], Hollis D[3], Prosnitz LR[1], Marks LB[1]

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Key Words: Breast neoplasm, Cardiac, Radiation

Abstract:

Purpose: To assess the incidence of regional cardiac perfusion defects and functional abnormalities in patients with left-sided breast cancer following RT with and without chemotherapy. To determine if the extent of RT-induced changes in regional cardiac perfusion is related to the volume of heart irradiated, cardiac function, or clinical sequelae.

Materials and Methods: Forty patients with left-sided breast cancer have undergone pre-treatment single photon emission computed tomography (SPECT) cardiac perfusion scans to evaluate regional myocardial perfusion and cardiac function by left ventricular ejection fraction (LVEF). Seventeen patients were treated with RT only and 23 patients were treated with Dox-based chemotherapy prior to RT. Risk factors for cardiac disease were obtained. At six month intervals patients have follow-up cardiac perfusion scans and a physical exam for a minimum of 2 years. Radiation doses and heart/left ventricle volumes were calculated on a computed tomography (CT) based 3-D treatment planning system (Plan University of North Carolina). Pre-RT and follow-up cardiac perfusion scans were registered to the dose distribution using image registration software. The relationship between changes in regional cardiac perfusion and RT dose was assessed.

Results: Six month follow-up cardiac perfusion scans have been obtained on 5 patients treated with RT only to the breast (no lymph nodes). The prescribed tangent RT dose was 46 Gy for all patients. The percent volume of heart and left ventricle irradiated at the 50% isodose line ranged from 1.8 to 10% and 2.9 to 19%, respectively. In 4 of 5 patients there were visibly detectable perfusion defects on the post RT scan in the inferior anterior region of the left ventricle that correlated with the tangential RT beams.

Correlating the dose distribution with the pre and post RT SPECT scans identified a dose-dependent reduction in the regional cardiac perfusion, R^2=.90. There was no evidence of a reduction in regional cardiac perfusion in the volume receiving 0-10 Gy, a 10% reduction in perfusion in the volume receiving 20 to 30 Gy, and a 20% reduction in perfusion in the volume receiving 40-50 Gy. There were no changes in the LVEF or clinical evidence of a cardiac event.

Conclusions: At six months follow-up, RT appears to cause dose-dependent regional cardiac perfusion defects in most patients with left-sided breast cancer. To date regional perfusion changes do not correlate with a change in LVEF or clinical cardiac events. This is an ongoing study and updated results will be reported including follow-up on patients treated with Dox and RT, and correlation of the volume of heart irradiated with the extent of perfusion defects.

This work was funded by Department of Defense Breast Cancer Research Grant, #BC972695.

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Duke University Medical Center
Curriculum Vitae

Revised: 4/27/99

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PUBLICATIONS IN REFEREED JOURNALS

1. Leith JT, **Harrigan (Hardenbergh)** P, Michelson S. Verhustian analysis of the growth of transplantable mammary tumors in sialoadenectomized mice. Cell Proliferation. 24, (6):587-592. 1991.

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GRANT SUPPORT

Department of Defense Breast Cancer Research Award. BC972695 - Pathophysiologic Impact of Chemotherapy and Radiation Therapy on the Heart of Patients Treated for Breast Cancer **PH Hardenbergh, Principal Investigator**. 1998-2001, $315,018 total costs.

Pilot project grant awarded from the DUMC SPORE Breast Cancer Grant entitled "Pathologic Impact of Chemotherapy and Radiation Therapy on the Heart of Patients treated for Breast Cancer. **PH Hardenbergh, Pricipal Investigator.** 1997-1998, $20,000 total costs.

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FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB243021
ADB262474
ADB284009
ADB257455
ADB257446
ADB261351
ADB259684
ADB282142
ADB285141
ADB272522
ADB284022
ADB283904

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